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QUINAGLUTE, CARDIOQUIN AND QUINIDINE SULFATE

Quinaglute Dura-Tab (Wynn), a sustained-release preparation of quinidine gluconate, is claimed to be "the first major advance in quinidine therapy in over 40 years," and to be "safer and better tolerated" than Quinidine Sulfate Tablets, USP, the standard drug for the prevention and treatment of cardiac arrhythmias. Another oral preparation, quinidine polygalacturonate (Cardioquin - Purdue Frederick), is claimed to have advantages over quinidine sulfate in "avoidance of local gastrointestinal irritation" and "more reliable and sustained rate of absorption."

Oral quinidine sulfate is usually effective in either acute or chronic arrhythmias (M. Sokolow and D. B. Perloff, Progr. Cardiov. Dis., 3:316, 1961). Where a very rapid effect is needed, or where medication cannot be taken by mouth, quinidine gluconate can be administered intramuscularly or, in the most urgent situations, intravenously. The size of the dose and the frequency of its administration depend on the seriousness of the arrhythmia and the rate of metabolism and excretion of quinidine; this rate varies in different patients, and the variation influences both the effects of the drug on cardiac action and its toxicity (cinchonism). The determination of both size and spacing of doses should be based on close clinical observation, frequent electrocardiograms, and, when necessary, the measurement of plasma quinidine levels.

BLOOD LEVELS - In clinical trials, the quinidine gluconate in the prolonged-action Quinaglute Dura-Tabs was absorbed more slowly than quinidine sulfate, the quinidine reaching a peak blood level in five hours as compared with two hours for quinidine sulfate or ordinary quinidine gluconate (E. Greif and J. Scheuer, J. Mt. Sinai Hosp., 27:612, 1960; S. Bellet, et al., AMA Arch. Int. Med., 100:750, 1957). The longer interval indicates that an insufficient proportion of the drug is available for immediate release so that it is more a "delayed-action" than a "sustained-release" product. The 24-hour blood level after a single dose of Quinaglute Dura-Tabs is higher than after a single comparable dose of quinidine sulfate, but the clinical importance of the difference is questionable, particularly since a bedtime dose of quinidine sulfate is usually effective for maintenance therapy.

As for the comparative toxicity of Quinaglute and quinidine sulfate, no differences were noted in one study (Greif and Scheuer, cited above). The authors state, "Both with quinidine sulfate and quinidine gluconate, severe gastrointestinal symptoms and associated weakness forced a discontinuation of these drugs. There was

no evidence that relatively higher doses of long-acting quinidine gluconate than of quinidine sulfate could be given before intolerable side actions appeared."

GASTROINTESTINAL EFFECTS - The main advantage claimed for Cardioquin is that it is as effective as quinidine sulfate, but "avoids local gastrointestinal irritation." This advantage has not been established by controlled clinical trials. Gastrointestinal symptoms may occur with small doses of quinidine salts as the result of either local gastrointestinal irritation or hypersensitivity; more often the symptoms occur only with larger doses of quinidine salts, as a result of the effects of the drug on the brain stem.

There is no evidence that other symptoms of cinchonism such as labyrinthitis, tinnitus, deafness, and central-nervous-system toxic symptoms such as diplopia, scotomata, and headache, are less likely to occur with either of the new preparations than with quinidine sulfate. Sudden fall in blood pressure (due to vasodilatation) is the most serious of the side effects of quinidine, and is more likely to occur with intramuscular or intravenous quinidine than with any oral preparation. Other cardiotoxic effects, such as ventricular tachycardia or fibrillation, may also occur.

In the conversion of auricular fibrillation to sinus rhythm, the short-acting quinidine sulfate is preferable to the longer-acting Quinaglute Dura-Tabs; the more rapid metabolism and excretion of quinidine sulfate make it easier to adjust dosage both upward to achieve adequate plasma levels and downward to control toxic reactions. Successful conversion has been achieved with Quinaglute Dura-Tabs, but this drug is best reserved for maintenance therapy after regular sinus rhythm is established. As compared with Cardioquin, quinidine sulfate is absorbed more rapidly and produces peak effects earlier.

DOSAGE - For conversion of auricular fibrillation to regular sinus rhythm, M. Sokolow and A. L. Edgar (Circulation, 1:576, 1950) found that 0.4 to 0.6 Gm. of quinidine sulfate every two hours for five doses produced an average peak blood level of 6 mg. per liter and was effective with most patients. For the prevention and treatment of the less serious arrhythmias such as premature auricular or ventricular extrasystoles or paroxysmal supra-ventricular tachycardias, doses of quinidine sulfate of 0.2 to 0.4 Gm. at two- to four-hour intervals (producing a plasma level of about 4 mg. per liter or less) are often effective in curbing the arrhythmia in six to 24 hours. The most satisfactory preparation for intramuscular injection is an 8% solution (0.8 Gm. in 10 cc.) of quinidine gluconate (Lilly). For intravenous administration, 10 cc. of quinidine gluconate solution (0.8 Gm. of drug) should be diluted to 50 to 100 cc. in saline or glucose solution and injected slowly at the rate of 1 to 2 cc. per minute.

In summary, quinidine sulfate is still the oral drug of choice for both conversion and maintenance therapy, though the other two drugs are probably effective for conversion if given in sufficient dosage, and all three can be used successfully for maintenance therapy. Cardioquin may be worth trying if local gastrointestinal irritation is believed to be a factor in limiting the use of quinidine sulfate. A daily maintenance dosage of quinidine sulfate (three 3-gr. tablets) costs the patient about 12¢; the equivalent dose of Quinaglute costs about 50¢ and of Cardioquin, about 40¢.

PYRIDIUM

The Medical Letter has received many inquiries from readers about phenyl-azo-diamino-pyridine (Pyridium - Warner, Chilcott), an azo dye originally introduced as an oral urinary antiseptic, but now used exclusively as a urinary-tract analgesic. As much as 65 per cent of the usual oral dose (0.4 to 0.8 Gm. per day) is excreted in the urine unchanged, imparting a reddish-orange color to an acid urine. Pyridium is used by itself and in combinations; it is often combined with antibacterial agents, as, for example, in Azo-Gantrisin (Roche), Azo-Kynex (Lederle), Azo-Mandelamine (Warner, Chilcott), and Azotrex (Bristol).

Both animal and clinical studies have been cited as evidence for the analgesic effectiveness of Pyridium. In one animal study, topical application of 0.1% to 0.25% Pyridium solution produced corneal anesthesia in rabbits (S. Krop, Anesth. & Analgesia, 25:110, 1946). In a clinical study, instillation of one ounce of 1% Pyridium solution into the bladder via the urethra was reported to have sufficient local anesthetic effect on the mucous membrane of the bladder and the urethra to permit painless cystoscopy (J. H. Morrissey and A. N. Spinelli, J. Urol., 44:381, 1940).

ANALGESIC DOSE - Many urologists, including O. S. Lowsley and T. J. Kirwin (Clinical Urology, Williams & Wilkins, 1956, 3rd ed., p. 983), are convinced of the analgesic effectiveness of Pyridium, and believe that in doses of 0.2 Gm. three times a day orally it is useful in relieving painful symptoms of urinary-tract infection. No controlled studies have, however, been carried out to test the validity of these empirical observations, and several Medical Letter consultants doubt that the drug has significant analgesic effect on the urinary tract.

Pain is a symptom known to be responsive to placebo medication, and it is possible that this drug (aided perhaps by the reddish color imparted to the urine) is an especially effective placebo. Whether the analgesic effects of Pyridium are due to pharmacologic action or to placebo effects can be determined only by controlled trial in which Pyridium is compared both with placebo and with standard analgesic measures such as warm sitz baths and the use of anticholinergic and analgesic or narcotic drugs.

SIDE EFFECTS - Unlike other pyridine compounds, Pyridium has not been definitely implicated as a cause of blood disorders. The possibility that it may be carcinogenic is, however, suggested by a study in which pellets of four parts cholesterol and one part Pyridium were implanted in the bladders of mice. The pellets produced tumors in four of 14 animals surviving after 30 weeks (two tumors were benign and two were carcinomas) (M. J. Allen, et al., Brit. J. of Cancer, 11:212, 1957). While the risk in humans is negligible in short-term therapy, it is a factor that should be considered with long-term therapy. The manufacturer warns that Pyridium is contraindicated in renal insufficiency or severe hepatitis.

For more certain relief from urinary distress, urologists depend primarily on the detection and correction of obstruction and other local factors which encourage infection or are responsible for pain. In many instances antibacterial agents may be required (see The Medical Letter, 2:93, 1960). If Pyridium is used, it should not be considered a substitute for specific surgical or antimicrobial therapy.

PHOTOSENSITIVITY REACTIONS TO DRUGS

Although photosensitivity reactions to drugs are not frequent, the summer months will undoubtedly see an increase in their incidence, and an awareness of the possibility of such reactions is important when certain drugs are administered or prescribed.

Among the drugs which are known to cause photosensitivity reactions are the thiazide diuretics; the anti-infective sulfonamides; antibiotics (especially demethylchlortetracycline [Declomycin - Lederle], chlortetracycline [Aureomycin - Lederle] and griseofulvin [Fulvicin - Schering; Grifulvin - McNeil; Griseofulvin - Ayerst]); such phenothiazines as chlorpromazine (Thorazine - SKF), promazine (Sparine - Wyeth), promethazine (Phenergan - Wyeth), and triflupromazine (Vesprin - Squibb); and methoxsalen (Oxsoralen - Elder; Meloxine - Upjohn). (Methoxsalen is used orally to increase tolerance to ultraviolet light, but it sometimes causes photoallergic reactions.)

Less frequently implicated as photosensitizers are barbiturates, salicylates, and oral para-aminobenzoic acid. (Para-aminobenzoic acid is used topically as an ultraviolet-absorbing barrier to prevent light reactions.)

THE SULFONAMIDES - Of the photosensitizers listed above, the thiazide diuretics and the sulfonamide anti-infectives are chemically related; and it is not unlikely that other sulfonamides, for example, the carbonic anhydrase inhibitors (Diamox - Lederle, and others), will occasionally have a photosensitizing effect. Tolbutamide, USP (Orinase - Upjohn), a sulfonylurea compound, has been suspect but not definitely implicated as a photosensitizer.

Light-induced reactions associated with the oral or parenteral use of drugs are usually either phototoxic or photoallergic, or a combination of both. The phototoxic reaction resembles exaggerated sunburn; the severity of the reaction is dependent on the dose of the sensitizing drug and the intensity of the exposure to ultraviolet light. The reaction is characterized by erythema with or without blistering. When the erythema subsides, residual tanning appears, as in ordinary sunburn.

PHOTOALLERGY - Photoallergic reactions depend on an antigen-antibody reaction, and require an incubation period of at least several days after exposure both to the drug and to light. The skin reaction takes the form of urticarial, papular, eczematous or lichen-planus-like lesions, without residual tanning. After initial sensitization, subsequent exposure produces a reaction in hours or even minutes.

Photosensitivity reactions caused by both Declomycin and Aureomycin are occasionally accompanied by transient destructive changes in nails exposed to light. Drug photosensitivity is seldom associated with serious systemic reactions, but it is generally advisable to use another drug when reactions occur. (Griseofulvin is the only photosensitizing drug for which an adequate substitute cannot be found.) If the patient avoids direct exposure to sunlight, however, he may be able to continue with the original medication; when exposure cannot be avoided, the use of a sun-screen cream or lotion may be helpful.

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